

# Genetic associations of variants of the high affinity receptor for immunoglobulin E in Wegener's granulomatosis

Marek Sanak, Daniel P. Potaczek, Jan Sznajd, Jacek Musiał, Andrzej Szczeklik

Department of Internal Medicine, Jagiellonian University Medical College, Kraków, Poland

## KEY WORDS

FcεRI, gene polymorphism, IgE receptor, Wegener's granulomatosis

## ABSTRACT

Immunoglobulin E (IgE) and the high affinity IgE receptor (FcεRI) have been suggested to contribute to the pathogenesis of autoimmune disorders. Their role in Wegener's granulomatosis (WG) are, however, poorly recognized. We sought a genetic association between laboratory markers for the disease, i.e. anti-proteinase 3 antibodies (anti-PR3), anti-myeloperoxidase antibodies, anti-cyclic citrullinated peptide antibodies, C-reactive protein (CRP), C3c and C4 complement components, and total serum IgE levels in WG subjects with common genetic variants of FcεRI subunits. Anti-PR3 and CRP and serum IgE levels showed significant associations, while complement components tended to be associated, with –18483A>C and/or –344C>T FCER1A (FcεRI α-subunit gene) polymorphisms. Moreover, a correlation between –109T>C FCER1B (FcεRI β-subunit gene) genotypes and serum IgE was observed. Both WG specific auto-antibodies and other blood inflammatory markers displayed correlations with serum total IgE levels and genetic variants of the high affinity receptor for this immunoglobulin. This observation suggests a functional relationship of FcεRI in the regulation of autoimmune response observed in WG.

**INTRODUCTION** Wegener's granulomatosis (WG) is a primary necrotizing vasculitis of unknown etiology, characterized by the presence of antineutrophil cytoplasmic antibodies (ANCA).<sup>1</sup> Genetic association studies have suggested that the variability of T-cell co-stimulatory molecule receptor cytotoxic T-lymphocyte antigen 4, interleukin-10 gene and human leukocyte antigens system may predispose to WG.<sup>2,3</sup> Elevated serum immunoglobulin E (IgE) levels have also been reported<sup>4,5</sup> among immunological alterations in WG patients, but their relevance to the vasculitis has not been established. Serum IgE represents only to a minute fraction of immunoglobulins, and is mostly bound to the high affinity receptor (FcεRI) present on mast cells, basophils and eosinophils. The receptor occupied by allergen-specific IgE molecules is responsible for anaphylaxis and possibly can also modulate the immunological response, because it is expressed on antigen presenting cells.<sup>6</sup> Moreover, the gene encoding for

IgE-binding α-subunit of the FcεRI (*FCER1A*) maps to chromosome 1q21-23, the region implicated in susceptibility to multiple autoimmune disorders and/or allergy.<sup>7</sup> Interestingly, altered expression of *FCER1A* has been observed in patients with systemic lupus erythematosus.<sup>8</sup>

**Working hypothesis** We investigated common genetic variants of genes coding for α- (*FCER1A*) and β-subunit (*FCER1B*) of FcεRI in WG. This genetic variability is located in the gene controlling region and was previously associated with elevated serum IgE in allergic subjects<sup>9,10</sup>, however there were no studies performed in subjects with autoimmune diseases. We wondered if genetic variability of these loci is correlated to quantitative inflammatory features in a moderately numerous but well characterized group of WG patients.

**MATERIALS AND METHODS** 30 consecutive subjects diagnosed with WG were enrolled

## Correspondence to:

Prof. Marek Sanak, MD, PhD,  
II Katedra Chorób Wewnętrznych,  
Uniwersytet Jagielloński, Collegium  
Medicum, ul. Skawińska  
8, 31-066 Kraków, Poland,  
phone: +48-12-430-52-66,  
fax: +48-12-430-52-03, e-mail:  
mmsanak@cyf-kr.edu.pl

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MD, PhD

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**TABLE 1** Clinical and laboratory characteristics of the patients (n = 30)

age (years)	50.6 ±13.03
sex (females/males)	15/15
skin involvement	11/n
joint involvement	17/n
urogenital involvement	19/n
lower respiratory tract involvement	18/n
upper respiratory tract and/or ear involvement	18/n
eye involvement	6/n
gastrointestinal involvement	7/n
cardiovascular involvement	8/n
neurological involvement	9/n
positive ANCA	26 <sup>a</sup> /n
positive ANCA currently or in the past	30/n
positive anti-PR3	21/n
anti-PR3 (RU/ml)	37.6 (9.46–98.18)
positive anti-MPO	2/n
positive ANA	15/n
positive aCCP	1/n
positive RF	6/n
CRP (mg/l)	4.33 (3.08–8.77)
C3c complement component (g/l)	1.26 (1.12–1.56)
C4 complement component (g/l)	0.28 (0.237–0.333)
logarithm of total serum IgE	1.73 ±0.49

Age and log-transformed IgE are means ± standard deviations, other measurements are medians (25<sup>th</sup>–75<sup>th</sup> percentile)

**a** including 18 c-ANCA (cytoplasmic), 3 p-ANCA (perinuclear), 3 a-flat-c-ANCA (atypical-flat), 1 c-ANCA/p-ANCA and 1 c-ANCA/p-ANCA/a-flat-c-ANCA cases

Abbreviations: aCCP – anti-cyclic citrullinated peptide antibodies, ANA – anti-nuclear antibodies, ANCA – anti-neutrophil cytoplasmic antibodies, anti-MPO – anti myeloperoxidase antibodies, anti-PR3 – anti-proteinase-3 antibodies, CRP – C-reactive protein, IgE – immunoglobulin E, RF – rheumatoid factor

to the study. A simple clinical symptoms assessment scale was used to record the systemic involvement by the disease. Patients characteristics are presented in **TABLE 1**. All the patients gave written informed consent to participate in the study and the Jagiellonian University Ethics Committee approved the study.

Laboratory measurements were performed in venous blood. The genotyping for *FCER1A* –18483A>C, –344C>T and –95T>C, and *FCER1B* –109T>C common variants was done by polymerase chain reaction amplification and restriction enzyme digestion as described previously.<sup>11,12</sup> Diagnostic ANCA were detected and classified as perinuclear (p-ANCA), cytoplasmic (c-ANCA) or atypical-flat c-ANCA (a-flat-c-ANCA) by indirect immunofluorescence (IIF, Euroimmun AG, Luebeck, Germany) using human neutrophils. Titer greater than 1:10 was considered positive. Specific autoantibodies against proteinase-3 (anti-PR3) or myeloperoxidase (anti-MPO) were measured by enzyme-linked immunosorbent assay (ELISA) (Euroimmun AG, Luebeck, Germany). The threshold of 20 RU/ml was used for positive samples. Anti-nuclear antibodies were detected

by IIF (Euroimmun AG, Luebeck, Germany) using the HEP-2 cell line and considered positive at titer greater than 1:160. Serum complement components C3c and C4, rheumatoid factor (threshold 15 IU/ml), C-reactive protein (CRP) and total serum IgE levels were measured by laser immunonephelometry (Dade Behring Marburg GmbH, Marburg, Germany). Anti-cyclic citrullinated peptide antibodies (aCCP) were assessed using ELISA (Euroimmun AG, Luebeck, Germany; threshold 5 RU/ml).

Age was referred in years as a mean ± standard deviation. Because other parametric variables significantly deviated from the normal distribution; CRP, C3c, C4, anti-PR3, anti-MPO, aCCP levels were reported as median and 25<sup>th</sup>–75<sup>th</sup> percentile. Comparisons of these parameters between arbitrary genotype classes were done using the non-parametric Mann-Whitney U-test. Total serum IgE levels were log-transformed and reported as log (IgE) mean ± standard deviation and compared between the groups using the unpaired Student's t-test. A *p* <0.05 was considered significant.

**RESULTS** Genotypes for *FCER1A* and *FCER1B* were in Hardy-Weinberg equilibrium and their frequencies did not differ from those published for Caucasians. The following frequencies were observed for *FCER1A*: –18483A>C (10 AA, 18 AC, 2 CC), –344C>T (9 CC, 19 CT, 2 TT), –95T>C (13 TT, 16 TC, 1 CC), and for *FCER1B* –109T>C (12 TT, 13 TC, 5 CC).

Both, –18483A>C and –344C>T *FCER1A* polymorphisms were related to total serum IgE and CRP (**TABLE 2**). In addition, –18483A>C polymorphism was associated with anti-PR3 levels. C3c and/or C4 complement components showed a statistical trend for a correlation with both *FCER1A* variants. Total serum IgE levels were also associated with –109T>C *FCER1B* polymorphism. None of the listed above genetic variants was associated with the severity of WG, assessed using a clinical symptoms scale. The *FCER1A* –95T>C genetic variant, which did not correlate with laboratory markers of WG, interestingly showed a significant association with cardiovascular manifestations of WG; 78.6% carriers of –95C variant (CC or TC) had cardiovascular symptoms, while in patients with –95TT genotype only 25% (*p* = 0.016).

**SUMMARY** Elevated total serum IgE levels have been already described in WG patients, however, the specific role of IgE has not been discussed because increased biosynthesis of immunoglobulins commonly coexists autoimmune inflammation. In this preliminary report we confirmed that genetic variants of the high affinity receptor for IgE correlate with its levels, which was previously demonstrated in allergic subjects.<sup>13</sup> Moreover, the same receptor variants seem to have an impact on WG specific laboratory markers and on inflammatory process of the disease.

**TABLE 2** Correlations between the high affinity IgE receptor variants and the measured biomarkers

Polymorphism	Quantitative trait	Values	p
<i>FCER1A</i> –344C>T		CC homozygotes (n = 9) vs. T-allele carriers (n = 21)	
	Total serum IgE <sup>a</sup>	1.35 ±0.04 vs. 1.91 ±0.11	0.0001
	CRP	8.63 (5.72–16.75) vs. 3.08 (3.08–6.29) mg/l	0.004
	Anti-PR3	98.18 (10.57–237.745) vs. 31.34 (2.91–78.80) RU/ml	NS
	C3c	1.42 (1.27–1.60) vs. 1.2 (1.03–1.45) g/l	0.09
	C4	0.33 (0.25–0.42) vs. 0.26 (0.23–0.31) g/l	0.06
<i>FCER1A</i> –18483A>C		AA homozygotes (n = 10) vs. C-allele carriers (n = 20)	
	Total serum IgE <sup>a</sup>	1.49 ±0.14 vs. 1.87 ±0.1	0.04
	CRP	8.46 (5.2–13.8) vs. 3.08 (3.08–6.91) mg/l	0.005
	Anti-PR3	143.5 (10.94–283.78) vs. 28.8 (2.87–70.67) RU/ml	0.049
	C3c	1.42 (1.31–1.59) vs. 1.19 (1.03–1.425) g/l	0.06
	C4	0.32 (0.24–0.41) vs. 0.26 (0.23–0.316) g/l	NS
<i>FCER1B</i> –109T>C		TT (n = 12) vs. C-allele carriers (n = 18)	
	Total serum IgE <sup>a</sup>	1.93 ±0.14 vs. 1.58 ±0.1	0.047

**a** log-transformed IgE: means ± standard deviations, other data: median (25th–75th percentile)

Abbreviations: anti-PR3 – anti-proteinase-3 antibodies, C3c – C3c complement component, C4 – C4 complement component, CRP – C-reactive protein, IgE – immunoglobulin E, NS – non-significant

Genetic variability of *FCER1A* was found to associate with chronic urticaria<sup>14</sup>, a disease with frequently an autoimmune background. However, finding the correlation between the levels of specific autoantibodies and non-specific inflammatory markers, and variants of the high affinity receptor for IgE in WG suggest that the underlying mechanism can be more complex than the receptor mediated control of IgE biosynthesis alone. One of plausible mechanisms is the activity of dendritic cells involved in the clearance of apoptotic neutrophils, which may be modulated by FcεRI in WG.<sup>6</sup> Recently functional FcεRI expression has been demonstrated on smooth muscle cells of the airways.<sup>15</sup> A potential induction of the receptor on vascular smooth muscle cells is another putative mechanism which requires further investigations. Furthermore, the alternative ANCA-mediated complement activation pathway was proposed to play a role in the pathogenesis of ANCA-associated diseases.<sup>16</sup> Therefore, relationships between FcεRI genetic polymorphisms and complement components, and anti-PR3 or anti-MPO circulating ANCA which closely associate with WG<sup>1,16</sup>, appear particularly interesting. It could be supposed that also *FCER1A* may be hypothetically involved in the ANCA-dependent complement activation mechanism.

In summary, while in line with previous reports on allergic diseases<sup>9-13</sup>, the current study on associations between *FCER1A/FCER1B* genetic variants and total serum IgE levels extends these observations to the disease-specific and inflammatory markers in WG. These correlations are difficult to interpret based on current knowledge and suggest the presence of an immunological mechanism modulating the autoimmune inflammatory response by the high affinity IgE receptor pathway. If the presence of such a mechanism could

be confirmed, new therapeutic modalities might be considered for WG, for example using anti-IgE neutralizing antibodies.

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